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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/367,013	08/05/1999	DEBORAH KNUTZON	CGAB-210-USA	3773

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EXAMINER	
NASHED, NASHAAT T	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/367,013	KNUTZON ET AL.	
	Examiner	Art Unit	
	Nashaat T. Nashed, Ph. D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 September 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *189-244,255-290 and 297* is/are pending in the application.

4a) Of the above claim(s) *189-214 and 285-290* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *215-244,255-284 and 297* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 14, 2004 has been entered.

Claims 215-244, and 255-284 and 297 are under consideration.

The amendment filed July 7, 2003 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: A nucleic acid hybridizes preferentially to the complement of the sequence depicted in SEQ ID NO: 1 at 50 degree Celsius in 60 mM Tris-C; (pH8.5) and 15 mM amonium sulfate and 2 mM magnesium chloride in new claim 297.

Applicant is required to cancel the new matter in the reply to this Office Action.

In response to the above objections, applicants traverse the above objection and argue that PCR is involves hybridization, and that example 3 recite a hybridization step with the conditions recited in claim 297.

Applicants' arguments filed 9/14/04 have been fully considered but they are not deemed to be persuasive. It true that a PCR experiment comprises the hybridization of a probe, about 30-50 nucleotides in length, to a template in solution. The main purpose of a PCR experiment is to increase the amount of a known full-length nucleic acid in a sample. In contrast, the hybridization method is an analytical method for the identification of nucleic acid sequences encoding desired gene. Also, it contains a visualization step, which does not exist in a PCR experiment. The claim is directed to a product by a known method in the art, which is not described in the specification. One of ordinary skill in the art would consider a hybridization experiment is different and distinct method from a PCR experiment.

Claim 297 is objected to because of the following informalities: "Tris-Cl" should be -----Tris-HCl----. Appropriate correction is required.

In response to the above objections, applicants traverse the above objection and argue that the term Tris-Cl is a term used and understood by persons of skill in the art.

Applicants' arguments filed 9/14/04 have been fully considered but they are not deemed to be persuasive. Tris-HCl is a term that is well-understood by one of skill in the art to mean N-N-N-tris(hydroxymethyl)-N-methylamonium chloride, see any Sigma

catalog. On the other hand, tris-Cl is not a known abbreviation or acronym of any chemical compound that is known to one of ordinary skill in the art. Applicants must correct this obvious typographical error in both the specification and the claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 275-284 and 297 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Regarding claims 275-284 and 297, they are directed to a method of producing oil with altered fatty acid composition comprising extracting said oil from microbial cell transformed with a nucleic acid which hybridizes "under hybridization condition suitable for sequencing" to SEQ ID NO: 1 wherein the nucleic acid encodes Δ-6-desaturase. The specification, however, fails to describe any hybridization experiment or conditions including those "suitable for sequencing". In fact the phrase, "under hybridization condition suitable for sequencing" does not appear any where in the specification. Said phrase is considered a new matter and should be removed from the claim. Given this new matter encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Regarding claim 297, it is directed to a method of producing oil with altered fatty acid composition comprising extracting said oil from microbial cell transformed with a nucleic acid which hybridizes under the condition of PCR experiment. The specification, clearly, fails to describe any hybridization conditions or experiment including those found in claim 297. Thus, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Claims 225-244, 265-284 and 297 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to methods of producing oil in stearidonic acid using microorganism transformed with the nucleic acid sequences encoding of SEQ ID NO: 2 including SEQ ID NO: 1 from *Mortierella alpina* for the reasons set forth in the prior Office actions mailed 10/21/01, 6/28/02, 12/31/02, and 10/6/03. The disclosure is enabling only for claims limited to methods of producing oil

enriched in stearidonic acid using microorganism transformed with the nucleic acid sequences encoding Δ-6-desaturase of SEQ ID NO: 2 and Δ-12-desaturase of SEQ ID NO: 4 from *M. alpina*. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. The claims are broader than the enablement provided by the disclosure with regard to all possible nucleic acid sequences which have 80% sequence homology to SEQ ID NO: 1, encoding an amino acid sequence that is 80% homologues to SEQ ID NO: 2, or having any number of deletion of SEQ ID NO: 1, or hybridizes under any condition to the nucleic acid sequence of SEQ ID NO: 1. Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses a general method of producing oil enriched with unsaturated fatty acid using a microbial cell transformed with any nucleic acid sequences which has 80% sequence homology to SEQ ID NO: 1, encoding an amino acid sequence which is 80% homologues to SEQ ID NO: 2, having any number of deletion of SEQ ID NO: 1, or any nucleic acid sequence from any biological source that hybridizes under any conditions to the nucleic acid sequence of SEQ ID NO: 1. The specification provides guidance and examples in the form of an assay to isolate and characterize the nucleic acid encoding Δ-6-desaturase of SEQ ID NO: 2 and Δ-12-desaturase of SEQ ID NO: 4 from *M. alpina* and their use in producing oil with enriched in unsaturated fatty acid from a culture of microorganism (see examples 1-8) and isolation and determining the amount of each unsaturated fatty acid in an oil fraction. While molecular biological techniques and genetic manipulation to make the transformed microbial cell are known in the prior art and the skill of the artisan are well developed, knowledge regarding the redesigning of 20% of the amino acid residues of the polypeptide of SEQ ID NO: 2 (91 amino acid residues) by deletion, insertion, substitution or combination thereof, while maintaining the Δ-6-desaturase activity, or identifying a nucleic acid sequence encoding a Δ-6-desaturase having 80% sequence homology to SEQ ID NO: 2 from any biological source is lacking. Thus, searching for a nucleic acid sequence having 80% homology to SEQ ID NO: 1, or encoding a polypeptide having 80% sequence homology to the amino acid sequence of SEQ ID NO: 1 is well outside the realm of routine experimentation and predictability in the art of success is extremely low. The amount of experimentation to identify a nucleic acid having 80% sequence homology to SEQ ID NO: 1, encoding a Δ-6-desaturase polypeptide having 80% sequence homology toe SEQ ID NO: 2, having any number of deletion mutation of SEQ ID NO: 1, or hybridizes under any conditions to SEQ ID NO: 1 is enormous. Since routine experimentation in the art does not include screening vast

numbers of genomic, cDNA or manmade DNA libraries, identifying a function of a protein product encoded by a nucleic acid isolated from said libraries, and develop a method to desaturate fatty acids between C6 and C7, where the expectation of obtaining the desired nucleic acid to utilize in the claimed method is unpredictable, the Examiner finds that one skilled in the art would require additional guidance, such as information regarding the biological source of the nucleic acid, the nucleic acid sequences of other Δ-6-desaturase polypeptide, the three dimension structure of the polypeptide of SEQ ID NO: 2, and the amino acid residues which can be inserted, deleted, substituted without adverse effect on the folding of the polypeptide into a functional desaturase. Without such guidance, the experimentation left to those skilled in the art is undue.

Applicants dismiss the examiner's arguments regarding the *prima facie* case of non-enablement and the requirement for evidence to support enablement for the full scope of the claimed invention as a boilerplate language. They argue that applicants have disclosed many methods for generating mutants of SEQ IDNO: 1 and 2, which the examiner acknowledged. Then, they further argue that it would not take undue experimentation to make 80% sequences homologues to SEQ ID NO's: 1 and 2.

Applicants' arguments filed 9/14/04 have been fully considered but they are not deemed to be persuasive. Enablement of a claimed invention is a statutory requirement under 35 U. S. C. 112, first paragraph. The requirements for evidence or serious scientific arguments to overcome a *prima facie* case of non-enablement are not a boilerplate. The examiner has set above, and in the previous Office actions, a *prima facie* case of non-enablement, explaining by sound scientific reasoning why a person of ordinary skill in the art would doubt that the guidance of the specification would not enable the practice of the full scope of the claimed invention without undue experimentation. Applicants have presented no evidence or, indeed, any serious arguments to establish the adequacy of the disclosure to enable the scope of the instant claims. Applicants merely assert that the disclosure of the nucleic acid sequences and the teaching of single mutations is sufficient enablement for the claims. The examiner continues to disagree with applicants' views. Enablement requirements for mutation of up to 20% of an amino acid sequence comprising 457 amino acid residues requires much more enablement than that required for two or three mutation. Applicant quotes the specification on page 47-48 as providing enablement for mutating up to 20% based on sequence alignment. Clearly, this is insufficient enablement for the claimed method. The amino acid sequences are not identical as indicated on page 48, first paragraph, and mutation in one part of the molecule may require additional mutation in other parts of the molecule to maintain the structural and functional integrity of the protein. Since three-dimensional structure of the polypeptide of SEQ ID NO: 2 is unknown, one of ordinary skill in the art would not be able to ascertain the spatial relationship between different residues or identify the catalytically important residues in SEQ ID NO: 2. With

regard to nucleic acid, the specification teaches away from natural occurring 80% sequence homologues of SEQ ID NO: 1 as the specification state on page 48, lines 17-23:

> "However, it should be noted that, although the amino acid sequences of Ma524 and the borage 86 were found to contain regions of homology, the base compositions of the cDNAs were shown to be significantly different. For example, the borage cDNA was shown to have an overall base composition of 60 % A/T, with some regions exceeding 70%, while Ma524 was shown to have an average of 44% A/T base composition, with no regions exceeding 60%."

Applicants' response have failed to explain why the disclosure of the nucleic acid of SEQ ID NO: 1 and the amino acid sequence of SEQ ID NO: 2 provide sufficient enablement for a nucleic acid that that is 80% homologues to SEQ ID NO: 1, encode a polypeptide having 80% sequence homologues to SEQ ID NO: 2, or to nucleic acid that hybridizes to any nucleic acid sequence under any conditions. For the reasons set for above and the previous Office action, the claims remain rejected.

Applicants could not come up with any support for any hybridization conditions in their specification. Instead, they filed Shibuya *et al.*, which teach the isolation of cDNA encoding a galactosidase from *Mortierella*. Applicants seem to argue that hybridization conditions are well known in the prior art, and even publications do not identify them any more. The examiner agrees that many hybridization conditions are known in the prior art and one of ordinary skill in the art would be able select among the known ones. Applicants should be reminded that there are no claims attached to a journal publication, and one of ordinary skill in the art does not have to assess the scope of any claims in any publication. The situation is much different in a patent application. The scope of the claimed method is determined by the hybridization conditions. A nucleic acid such as SEQ ID NO: 1 is capable to hybridize to any other nucleic acid sequence under some hybridization conditions, and therefore, the hybridization language does not limit the claim.

Claims 275 and 297 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

(a) The phrases "hybridizes preferentially to the complement of the sequence depicted in SEQ ID NO: 1 under hybridization conditions suitable for sequencing said complement" in claim 275 renders the claim indefinite and confusing, respectively, because the resulting claim does not clearly

set forth the metes and bounds of the patent protection desired. Since nucleic acid are known to hybridize to any other nucleic acid sequence under different conditions, the nucleic acid sequence of SEQ ID NO: 1 is expected to hybridize to any nucleic acid sequence. Thus, the claim is considered indefinite. Since the specification does not contain any specific hybridization conditions, the claim can't be amended to obviate this rejection. The new phrase "under hybridization conditions suitable for sequencing said complement" is not defined or found in the specification, and one of ordinary skill in the art would not know its meaning. The phrase constitutes a new matter and should be deleted.

(b) Claims 276-284 are included in this rejection and do not cure the deficiencies of the claims from which they depend.

Applicants argue that there is no scientific bases for the examiner assertion that nucleic acid are known to hybridize to any other nucleic acid under different conditions. Also, they argue that the claims recite, "hybridizes preferentially" which would eliminate non-specific hybridization.

Applicants' arguments filed 9/14/04 have been fully considered but they are not deemed to be persuasive. Hybridization condition are classified in the prior art under, at least, three categories based the salt concentration, temperature, the amount of organic solvent such as formamid to high, medium, and low stringent conditions. Among each category, there are several known sets of conditions in the prior art known as high, medium, or low stringent. Since the result of a hybridization experiment would vary with the conditions used, one of ordinary skill in the art would not know the metes and bound of the claimed invention unless an exact hybridization conditions are defined by the claim.

(c) The phrase "nucleic acid hybridizes preferentially to the complement of the sequence depicted in SEQ ID NO: 1 at 50 degree Celsius in 60 mM Tris-Cl (pH8.5) and 15 mM amonium sulfate and 2 mM magnesium chloride" in claim 297 renders the claim indefinite and confusing, respectively, because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. In the previous Office action the abbreviation Tris-Cl is thought to be a typographical error, but apparently the applicants thought otherwise. Thus, the claim is also confusing because one of ordinary skill in the art would not know the meaning of Tris-Cl. The specification describes the above condition for PCR experiment and not for hybridization conditions, and thus, the phrase is considered new matter. For examination purposes only, the conditions are eliminated from the claim.

Applicants argue that the phrase is specific and therefore, indefiniteness has not been established.

Applicants' arguments filed 9/14/04 have been fully considered but they are not deemed to be persuasive. The clause "hybridizes preferentially" is not defined in the specification, and one of ordinary skill in the art would not distinguish between what is intended to be preferentially and what is not.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 215-244, 255-284 and 297 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, and 4-12 of U.S. Patent No. 6,459,018 ('018). Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 1, and 4-12 are directed to a method of increasing unsaturated fatty acids in plants by introducing Δ-6-desaturase to a plant and harvest the plant oil. Since one of ordinary skill in the art would have been motivated to harvest the oil with enhanced amount unsaturated fatty acids from microorganism such as yeast because of the ease of fermentation of said microorganism, it would have been obvious to one of ordinary skill in the art to transform a yeast cell with the nucleic acid of SEQ ID NO: 1 of the instant application, ferment the yeast, and isolate the oil produced from the fermentation by well known methods in the art (claims 215-244, 255-284 and 297).

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is 571-272-0934. The examiner can normally be reached on MTTF.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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